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Histologic Staging in Malignant Melanoma: Cross-Sectional Area Revisited

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Background and Objectives: Tumor thickness is considered the single most important predictor of survival in clinically localized malignant melanoma. A recent study found tumor volume a more sensitive predictor of survival than thickness. Volume measurement, however, is complicated, time consuming, and based on biologically imprecise mathematical models of tumor configuration. This report compares the prognostic power of cross-sectional area (CSA), a simpler measurement than volume, with tumor thickness.

Methods: Forty-five patients with clinically localized malignant melanoma and a minimum 5-year follow-up post excision with negative resection margins were retrospectively followed for disease recurrence or death. Digitalized histologic images of each tumor were made from the original pathology slides and stored on a compact disc. Maximum tumor thickness and CSA were calculated for each primary melanoma using an image analysis program and compared for predictive accuracy of 5-year survival.

Results: CSA was positively correlated with maximum tumor thickness ($r = 0.76$). Both measures had a similar predictive accuracy for survival. Patients with melanomas less than 8 mm^2 had superior 5-year (94%) and disease-free survival rates (78%) compared to patients with melanomas exceeding 8 mm^2 (5-year survival, 62%; 5-year disease-free survival, 23%).

Conclusions: CSA is an easily calculated measurement that is as predictive for 5-year survival as is Breslow's thickness. Prospective assessment of CSA is warranted. *J. Surg. Oncol. 1998;69:83–87.*

KEY WORDS: malignant melanoma; cross sectional area; prognosis

INTRODUCTION

Since Breslow's [1] landmark article relating tumor depth to prognosis, maximum tumor thickness has remained the single most important predictor of metastatic potential and patient survival in clinically localized malignant melanoma. Such a measurement relates the vertical component of a given tumor's growth to its likelihood of distant spread. While thicker tumors (increased vertical growth activity) generally have poorer clinical outcomes, relatively thin lesions are not infrequently seen to behave aggressively as well [2].

Bidimensional analysis of tumor configuration may contribute to prognostic sensitivity. This preliminary study was designed to examine the role of cross-sectional

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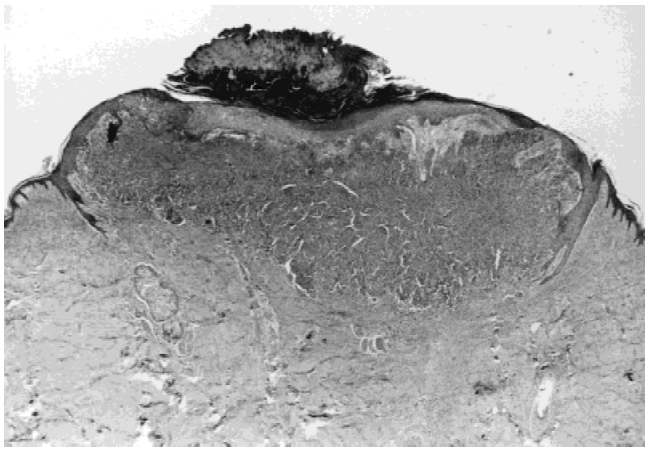

Fig. 1. Photomicrograph of nodular malignant melanoma (H & E, ×40).

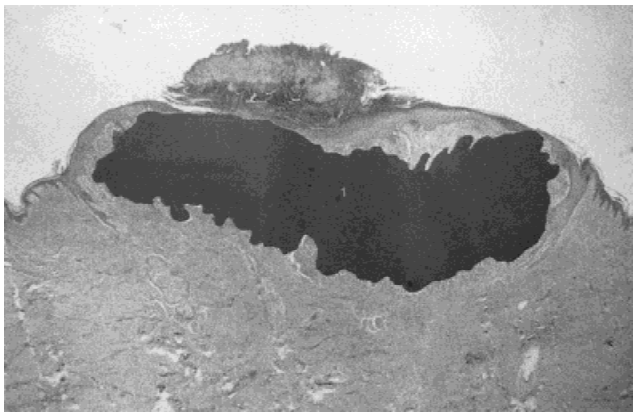

Fig. 2. Same lesions as in Figure 1 digitized onto compact disc and projected onto computer screen with melanoma cells circumscribed and CSA highlighted and measured by software program.

area (CSA) as a predictor of outcome and survival in this increasingly prevalent disease.

MATERIALS AND METHODS

Patient Selection

Clinic charts of 135 consecutive patients seen at the Kingston Regional Cancer Centre between 1987 and 1989 with clinical stage one malignant melanoma were reviewed. Patients meeting the following criteria were studied: clinically localized disease at presentation, excisional biopsy with negative margins, superficial spreading or nodular pathology, availability of original pathology slides for review, and minimum 5- year follow-up.

Clinical Outcome

Overall 5-year and disease-free survival rates (defined as lack of evidence for local or regional recurrence or metastatic disease) were recorded.

Pathologic Assessment

Routine haematoxylin and eosin or haematoxylin phyloxine saffron peroxidase (HPS) stained sections of each excisional biopsy specimen were reviewed. The pathologic type of melanoma (i.e., superficial spreading or nodular), and maximum tumor thickness (i.e., Breslow's thickness) were noted. Tumor CSA was measured from the slide containing the thickest portion of melanoma, using the following technique; each tumor was photographed at a low magnification of 20 or 40× magnification (Fig. 1). Slides of larger lesions required more than one photograph. These images were then digitized and stored on a photo compact disc. CSA measurement for each melanoma was calculated using a commercially available measurement software package (SigmaScan Image, Jandel Corporation, San Rafael, CA). Area in pixels was calculated automatically after each tumor periphery was circumscribed on the computer screen using the mouse (Fig. 2). Raw data in pixels were converted to square millimeters using a conversion factor derived from measurement of a known area. Measurements were done such that the researcher was blinded as to patient outcome.

Data Analysis

CSA and Breslow's thickness measurements were divided into quartiles when comparing their association with overall and disease-free survival rates at 5 years. Predictive accuracy, with 95% confidence intervals, was calculated for Breslow's thickness and CSA using the median as the cutoff point to balance the size of the comparison groups. Values for both measures from patients who did not survive 5 years were compared and tested using the Kruskall-Wallis test. To determine whether CSA improved the ability of Breslow's thickness to predict treatment failure, multiple logistic regression analysis was conducted using any adverse event as the dependent variable and log-transformed values for CSA and Breslow as the independent variables.

RESULTS

Of the 135 charts reviewed, only 45 patients satisfied the study criteria. The most significant problem was our inability to obtain original histologic material from the various outlying medical centers referring patients to the Regional Cancer Centre. In addition, those with advanced disease at presentation were excluded as were patients for whom complete data within the first 5 years following diagnosis were unavailable. Superficial spreading and nodular melanomas only were considered and each lesion had to be completely contained within the excisional biopsy specimen. Study patients included 17 women and 28 men with an overall average age of 50

TABLE I. Malignant Melanoma CSA: Range of Values by Quartile

Quartile	n	Breslow's thickness (mm)	CSA (mm^2)
1	11	0.30–0.75	0.19–2.12
2	11	0.76–1.30	2.13–4.38
3	11	1.31–2.10	4.39–8.07
4	12	2.11–8.20	8.08–38.22

years (range 22–84 years). There were 12 nodular and 33 superficial spreading melanomas. Most lesions were on the trunk (n = 21), with fewer involving the head or neck (n = 9), lower limb (n = 8), and upper limb (n = 7).

Tumor thickness ranged from 0.30 to 8.20 mm. CSA measurements ranged from 0.19 to 38.22 mm^2. For statistical comparison, the data were arranged from the smallest to largest for both tumor thickness and CSA and then divided into four equally sized quartiles. The range of values by quartile is shown in Table I. There was a strong positive correlation between maximum tumor thickness and CSA (r = 0.76; Fig. 3).

Overall 5-year survival is plotted against patient quartile in Figure 4. Death within 5 years of diagnosis was associated with greater tumor thickness ($P = 0.03$) and CSA ($P = 0.03$). Five-year disease-free survival (absence of local, regional, or distant metastatic spread or death) is plotted against quartile in Figure 5. Occurrence of an adverse outcome within 5 years was also associated with greater tumor thickness ($P = 0.0004$) and CSA ($P = 0.002$).

Predictive accuracy for various adverse outcomes is shown in Table II. Tumor thickness and CSA measurements were similar in their association with disease recurrence, metastasis, or death. Similarly, using multiple logistic regression analysis, Breslow's thickness significantly predicted treatment failure in terms of any adverse outcome (n = 20, $P = .01$), whereas CSA made no significant additional contribution ($P = .85$).

Despite the positive correlation between tumor thickness and CSA within the population studied, there was a standard deviation that allowed for a range of Breslow's thickness measurements for any given level of CSA. Where this seemed significant from a prognostic perspective was in those cases with a CSA more than 8.00 mm^2 which represented a threshold after which outcome was markedly affected. Figure 6 depicts overall and disease-free survival at 5 years above and below the 8 mm^2 threshold in CSA. CSA over 8 mm^2 clearly separated poorer outcomes ($P = .02$ for survival and $P = .0009$ for disease-free survival).

DISCUSSION

Since Breslow's landmark work in 1970, many studies have validated the prognostic importance of tumor thickness in malignant melanoma [3,4]. Maximum tumor thickness, as measured from the granular layer of the epidermis, remains the single most important predictor of metastasis and patient survival in clinically localized (stage 1) disease. However, some have recently suggested that tumor volume may be a more sensitive predictor of survival [5–7]. Friedman et al. [6] found that tumor volume was superior to thickness in predicting survival in 35 patients with stage 1 disease. Their method for determining tumor volume was complicated, time consuming, and involved biologically imprecise mathematical assumptions pertaining to tumor configuration within the subcutis. Earlier, Gebhart and Knobler [7] devised a computer- assisted volumetric analysis to calculate the total number of neoplastic cells in cutaneous melanoma. While reliable, they also found their technical system and method of measurement time consuming and too labor intensive. They discontinued the study after three specimens, concluding that volumetric analysis did not improve prognostic sensitivity over tumor thickness.

Accepting that there may be an inherent advantage of multidimensional over unidimensional tumor analysis, we have reexamined the role of CSA as a predictor of outcome in stage 1 malignant melanoma. Breslow [1] himself initially commented on the application of area measurements in his original work, having roughly calculated CSA from measurements of maximal tumor depth and diameter. Keeping in mind the need for technical accuracy, ease of measurement, and reproducibility, we have devised a bidimensional analysis that seems to at least share the prognostic power of Breslow's thickness. The current wide application of personal computers and the relative ease with which one can make computer-assisted measurements on digitized images of histologic specimens using commercially available software renders measurement of CSA feasible. Area measurements were easy to perform on routinely sectioned and stained slides of tumor. Measurements were accurate and reproducible and did not assume a model of tumor shape and distribution within the integument.

Since inception of this study, a more practical system for digitizing histologic slides directly onto the computer screen has become available, obviating the step of digitizing the image onto a compact disc. Furthermore, special staining for melanoma cells (S100 protein, HMB-45), which would exclude nonneoplastic stromal and inflammatory cells and nonviable necrotic tissue, could make tumor area measurements even more accurate. Indeed, this technology could be adapted to calculate tumor volume. However, the procedure would still be somewhat labor intensive. Any study assessing its prognostic relevance must necessarily be prospective as well as methodologically rigorous in the standardization of histologic sectioning and slide preparation for purposes of computer integration and calculation of volume.

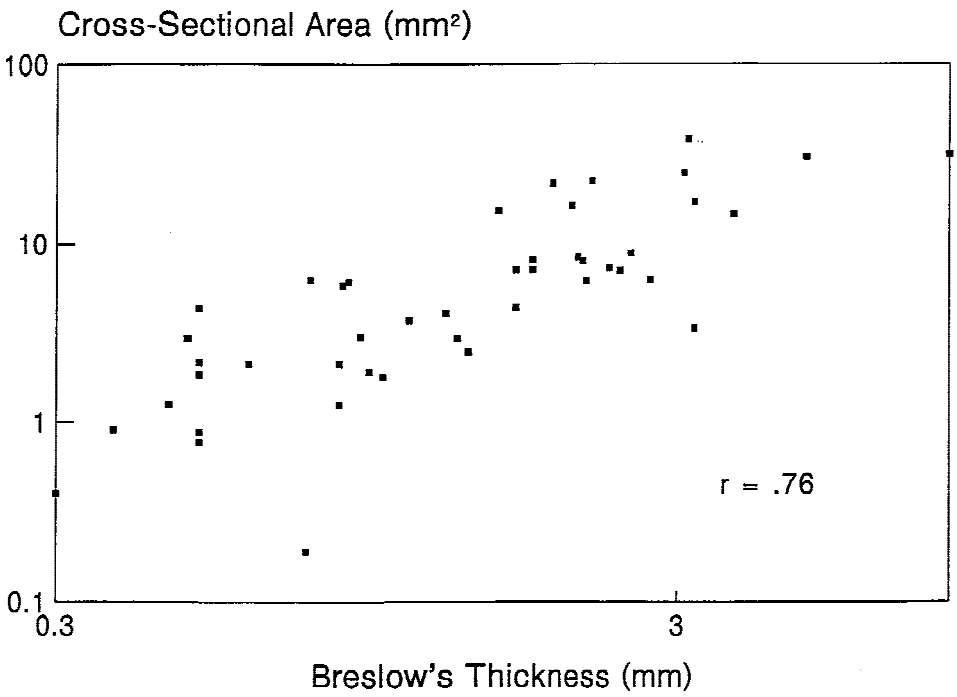

Fig. 3. Log plot of the relationship between CSA and Breslow's thickness. The two measures are highly correlated (r = .76).

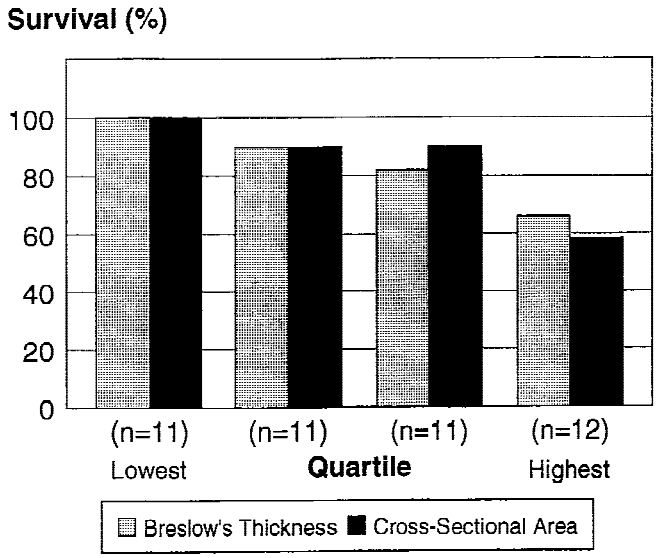

Fig. 4. Five-year survival by quartile of Breslow's thickness and CSA. Death within 5 years of diagnosis was associated with greater tumor thickness (P = .03) and CSA (P = .03).

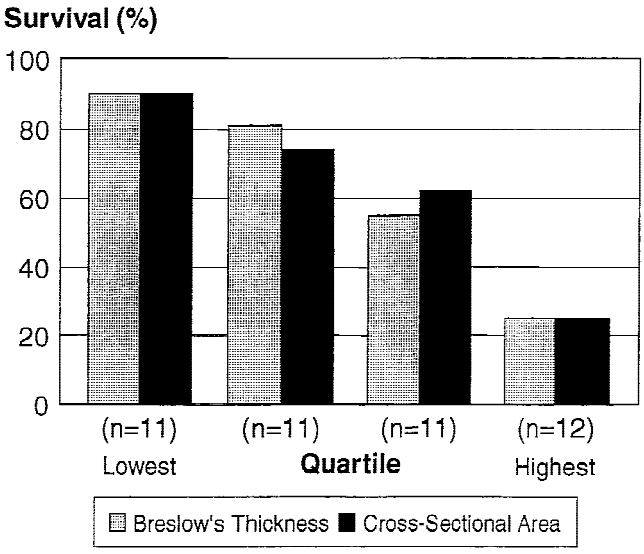

Fig. 5. Five-year disease-free survival by quartile of Breslow's thickness and CSA. Occurrence of an adverse outcome within 5 years of diagnosis with greater tumor thickness (P = .0004) and CSA (P = .002).

Although CSA has not been shown to be superior, no other easily attained measure has parallelled Breslow's thickness as a predictor of outcome in stage 1 malignant melanoma. There was a strong correlation between CSA and maximal tumor thickness. Both measurements were comparable in predicting recurrence and survival within the first 5 years after diagnosis. Presumably, a qualitatively similar relation might exist between CSA and tumor volume or mass. Indeed, we have identified a threshold CSA (8.0 mm^2) that, once reached, is associated with a significantly worse outcome compared to those with smaller lesions.

Prospective studies are warranted in order to avoid the recall bias inherent in retrospective reviews. They will ensure a representative and comprehensive patient population from which we can determine whether CSA provides improved prognostic sensitivity either alone or in

TABLE II. Malignant Melanoma: Predictive Accuracy for Disease-Free Survival of Breslow's Thickness and CSA

	Breslow's thickness (%)	CSA (%)
Local recurrence	64 (50–78)[a]	64 (50–78)[a]
Regional recurrence	69 (55–83)[a]	64 (50–78)[a]
Metastasis	62 (48–76)[a]	62 (48–76)[a]
Death	60 (46–74)[a]	60 (47–74)[a]

[a]95% Confidence intervals.

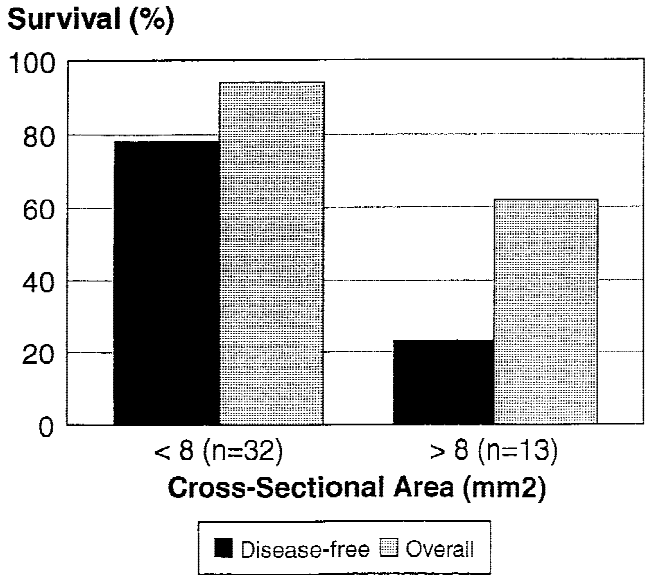

Fig. 6. Five-year disease-free survival and overall survival by CSA. Tumor areas exceeding 8 mm^2 were associated with a poorer survival ($P < .05$).

combination with maximum tumor thickness. This may permit better identification of patients or subsets of patients with more aggressive disease who may benefit by more directed therapeutic intervention.

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